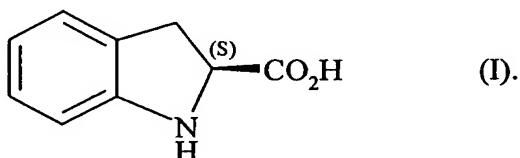


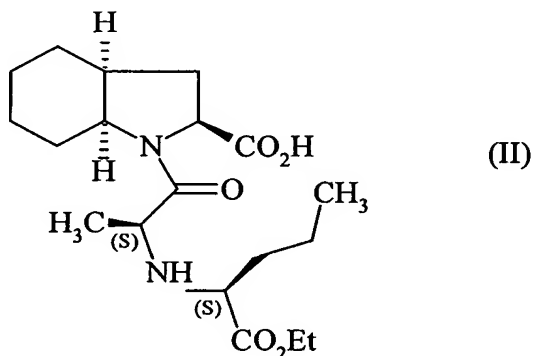
**NEW PROCESS FOR THE SYNTHESIS OF (2S)-INDOLINE-2-CARBOXYLIC  
ACID, AND APPLICATION IN THE SYNTHESIS OF PERINDOPRIL**

The present invention relates to a process for the synthesis of (2S)-indoline-2-carboxylic acid, and to its application in the synthesis of perindopril and pharmaceutically acceptable salts thereof.

More specifically, the present invention relates to a new process for the industrial synthesis of (2S)-indoline-2-carboxylic acid of formula (I) :



The compound of formula (I) obtained according to the process of the invention is useful in the synthesis of perindopril of formula (II) :



and in the synthesis of pharmaceutically acceptable salts thereof.

Perindopril and salts thereof have valuable pharmacological properties.

Their principal property is that of inhibiting angiotensin I converting enzyme (or kininase II), which allows, on the one hand, prevention of the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II (a vasoconstrictor) and, on the

other hand, prevention of the degradation of bradykinin (a vasodilator) to an inactive peptide.

Those two actions contribute to the beneficial effects of perindopril in cardiovascular diseases, more especially in arterial hypertension and heart failure.

- 5 Perindopril, its preparation and its use in therapeutics have been described in the European patent specification EP 0 049 658.

In view of the pharmaceutical value of this compound, it has been important to be able to obtain the intermediate of formula (I) by an effective synthesis process that allows the (S) enantiomer to be obtained selectively in a very good yield and with excellent purity.

- 10 Some methods for the preparation of the compound of formula (I) are already known.

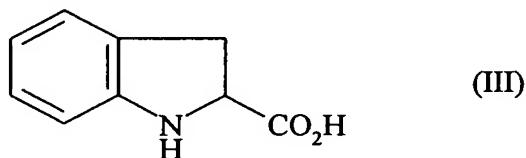
Thus, the patent specifications EP 0 308 339 and EP 0 308 341 describe obtaining (2S)-indoline-2-carboxylic acid by resolution of racemic indoline-2-carboxylic acid using (R)- $\alpha$ -methylbenzylamine. The (R)- $\alpha$ -methylbenzylamine salt of (2S)-indoline-2-carboxylic acid is isolated by fractional crystallisation, then acidified to yield the compound of  
15 formula (I).

That method has the advantage of using a starting material and reagents that are reasonably priced and very readily accessible.

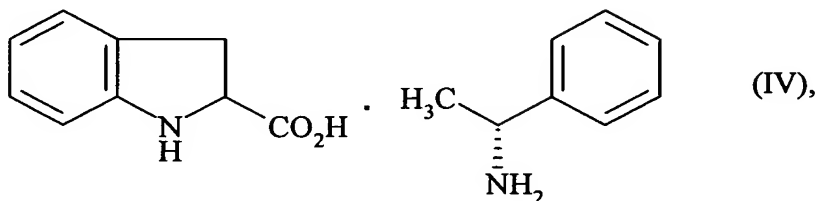
On the other hand, the yield of the compound of formula (I) using that method is only 35 %.

- 20 The Applicant has now developed a process for the synthesis of the compound of formula (I) in which the (2R) isomer, which is formed during the course of the resolution reaction, is recycled. The process developed in that way makes it possible to obtain the compound of formula (I) in a yield, starting from racemic indoline-2-carboxylic acid, that ranges from 50 % to 70 %, according to the number of recycling operations carried out.

More specifically, the present invention relates to a process for the synthesis of the compound of formula (I) which is characterised in that racemic indoline-2-carboxylic acid of formula (III) :

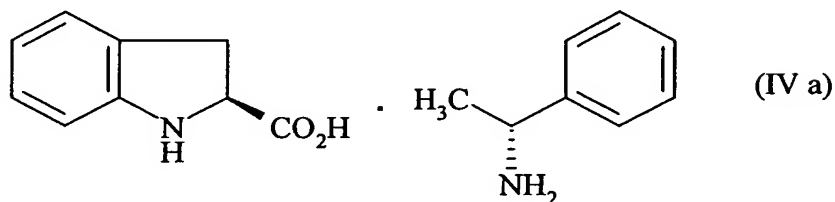


5 is reacted with a chiral amine  
to yield the salt of formula (IV) :



which is filtered off, and there being isolated :

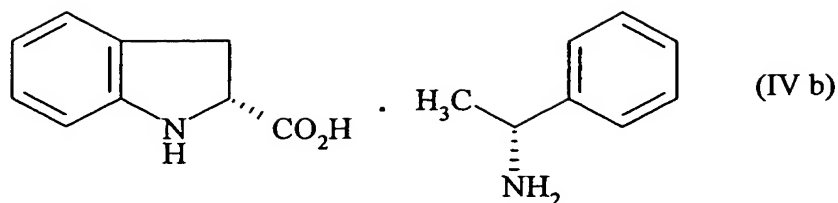
- on the one hand the (2S) isomer of formula (IV a) :



10 in the form of crystals,

which compound of formula (IV a) is then treated with hydrochloric acid to yield  
the compound of formula (I),

- 15
- and on the other hand a mixture of the (2S) isomer of formula (IV a) and the (2R) isomer of formula (IV b) in which the (2R) isomer predominates:



by evaporation of the filtrate,  
 which mixture is then treated with hydrochloric acid to yield a mixture of (2R)-  
 indoline-2-carboxylic acid and (2S)-indoline-2-carboxylic acid in which the (2R)  
 acid predominates,

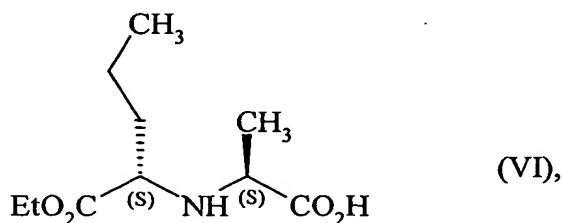
which is racemised by reaction with sodium hydroxide solution,  
 at a temperature of from 140 to 200°C,  
 under a pressure of from 5 to 15 bars,  
 to yield, after isolation, the compound of formula (III), with which the series of  
 operations described above is repeated,

then, after having carried out from 2 to 6 cycles, all the portions made up of the compound  
 of formula (I) are combined.

The compound of formula (I) is thereby obtained in a yield ranging from 50 % to 70 %,   
 according to the number of cycles carried out.

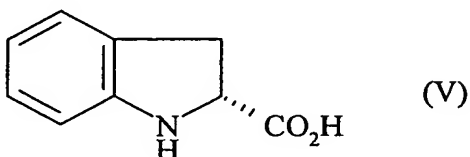
Its chemical and enantiomeric purity is very good, which makes its use in the synthesis of  
 perindopril of formula (II) especially advantageous.

By way of illustration, the catalytic hydrogenation of the compound of formula (I) obtained  
 according to the process of the invention, followed by coupling of the (2S,3aS,7aS)-  
 perhydroindole-2-carboxylic acid so obtained with the compound of formula (VI) :

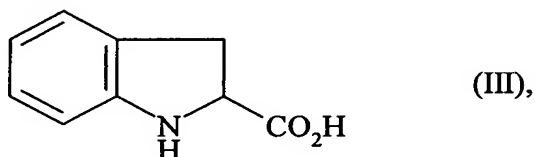


allows perindopril of formula (II) to be obtained in very satisfactory purity and yield.

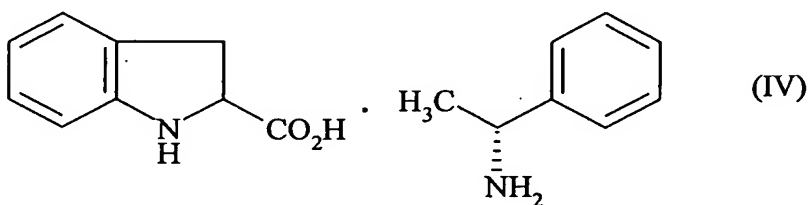
The present invention relates also to a variant of the above process in which there is reacted (2R)-indoline-2-carboxylic acid of formula (V) :



which is racemised by reaction with sodium hydroxide solution,  
at a temperature of from 140 to 200°C,  
under a pressure of from 5 to 15 bars,  
to yield, after isolation, the compound of formula (III) :

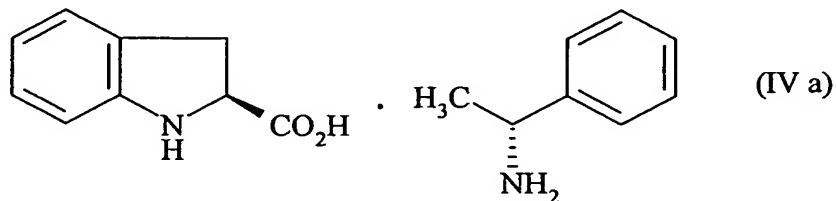


which is reacted with a chiral amine  
to yield the salt of formula (IV) :



which is filtered off, and there being isolated :

- on the one hand the (2S) isomer of formula (IV a) :

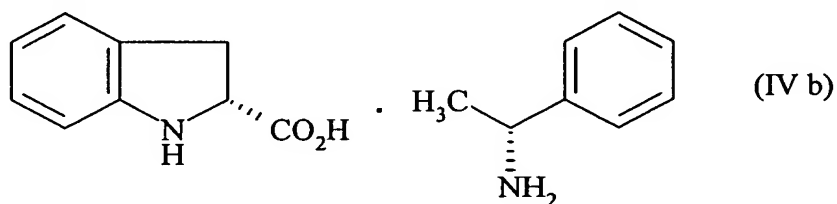


in the form of crystals,

which compound of formula (IV a) is then treated with hydrochloric acid to yield the compound of formula (I),

5

- and on the other hand a mixture of the (2S) isomer of formula (IV a) and the (2R) isomer of formula (IV b) in which the (2R) isomer predominates :



by evaporation of the filtrate,

10

which mixture is then treated with hydrochloric acid to yield a mixture of (2R)-indoline-2-carboxylic acid and (2S)-indoline-2-carboxylic acid in which the (2R) acid predominates,

with which there is repeated, if desired, the series of operations described above,

15

then, after having carried out from 1 to 6 cycles, all the portions made up of the compound of formula (I) are combined.

Among the chiral amines that can be used in the process according to the invention or its variant there may be mentioned, without implying any limitation, (R)- $\alpha$ -methylbenzylamine, 1-(1-naphthyl)-ethylamine, ephedrine,  $\alpha$ -chymotrypsin, sec-butylamine, 1-amino-2-methylbutane, N,N-dimethyl-1-phenylethylamine, 1-cyclohexylethylamine, cycloserine, 2-(methoxymethyl)-pyrrolidine,  $\alpha$ -dimethylamino- $\epsilon$ -caprolactam, isobornylamine, 1-(4-nitrophenyl)-ethylamine,  $\alpha$ -amino- $\epsilon$ -caprolactam, 2-amino-1-butanol, 1-amino-2-propanol, cinchonidine, cinchonine, N-methyl-ephedrine, phenylalaninol, quinidine, valinol,  $\alpha$ -phenyl-glycinol, leucinol.

25

The preferred chiral amine is (R)- $\alpha$ -methylbenzylamine.

“Mixture in which (2R) predominates” is understood to mean a mixture of (2R) and (2S) isomers in which the (2R) isomer forms the majority of the mixture.

The Example below illustrates the invention.

5     **EXAMPLE :     (2S)-indoline-2-carboxylic acid**

Step A :     *Resolution of racemic indoline-2-carboxylic acid*

3.7 kg of (R)- $\alpha$ -methylbenzylamine are added to a solution of 5 kg of indoline-2-carboxylic acid in ethanol and then the mixture is stirred for 2h and filtered.

10           Step A<sub>1</sub> :     *(2S)-indoline-2-carboxylic acid*

The white precipitate collected in Step A is recrystallised from isopropanol and then dissolved in 13 litres of water, and 12 litres of a 1N hydrochloric acid solution are added. After stirring for 2h, the precipitate is filtered off and then washed and dried to yield (2S)-indoline-2-carboxylic acid (« 1<sup>st</sup> portion ») in the form of crystals (1.80 kg) with a  
15     chemical purity of 98 % and an enantiomeric purity greater than 99.5 %.

Step A<sub>2</sub> :     *Indoline-2-carboxylic acid (mixture in which (2R) predominates)*

The filtrate collected in Step A is evaporated and the residue obtained is dissolved in 13 litres of water and then 12 litres of a 1N hydrochloric acid solution are added. After stirring for 2h, the precipitate is filtered off and then washed and dried to yield  
20     indoline-2-carboxylic acid in the form of a mixture of the (2R) and (2S) enantiomers (2.6 kg) in which the (2R) enantiomer predominates.

Step B :      *Racemisation*

Introduce into an autoclave the precipitate obtained in Step A<sub>2</sub> (2.6 kg), and then 12 litres of water and 3.1 litres of an 8.65N sodium hydroxide solution, then heat at 170°C for 3h under a pressure of 7 bars.

5      The reaction mixture is subsequently brought to ambient temperature and then transferred to a reactor, and concentrated hydrochloric acid is subsequently added until a pH of 3.4 is reached while maintaining the temperature between 20 and 25°C.

The mixture is then stirred for 1h and the precipitate is subsequently filtered off, washed and dried to yield racemic indoline-2-carboxylic acid in a yield of 90 % (2.34 kg).

10

Step C :      *Recycling of indoline-2-carboxylic acid*

The racemic indoline-2-carboxylic acid obtained in Step B (2.34 kg) is resolved according to the procedure in Step A.

15      The (R)- $\alpha$ -methylbenzylamine salt of (2S)-indoline-2-carboxylic acid so formed is isolated and then treated with hydrochloric acid according to the procedure in Step A<sub>1</sub> to yield (2S)-indoline-2-carboxylic acid (« 2<sup>nd</sup> portion ») in the form of crystals (0.84 kg) having a chemical purity of 98 % and an enantiomeric purity greater than 99.5 %.

The 1<sup>st</sup> portion, obtained in Step A<sub>1</sub>, and the 2<sup>nd</sup> portion, obtained in Step C, are then combined.

20      (2S)-indoline-2-carboxylic acid is thereby obtained in a total yield of 52.8 %, a chemical purity of 98 % and an enantiomeric purity greater than 99.5 %.